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TOPICAL HAZARD EVALUATION OF CANDIDATE INSECT REPELLENT, AI3-36--ETC(U)  
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USAEHA-51-0818-77

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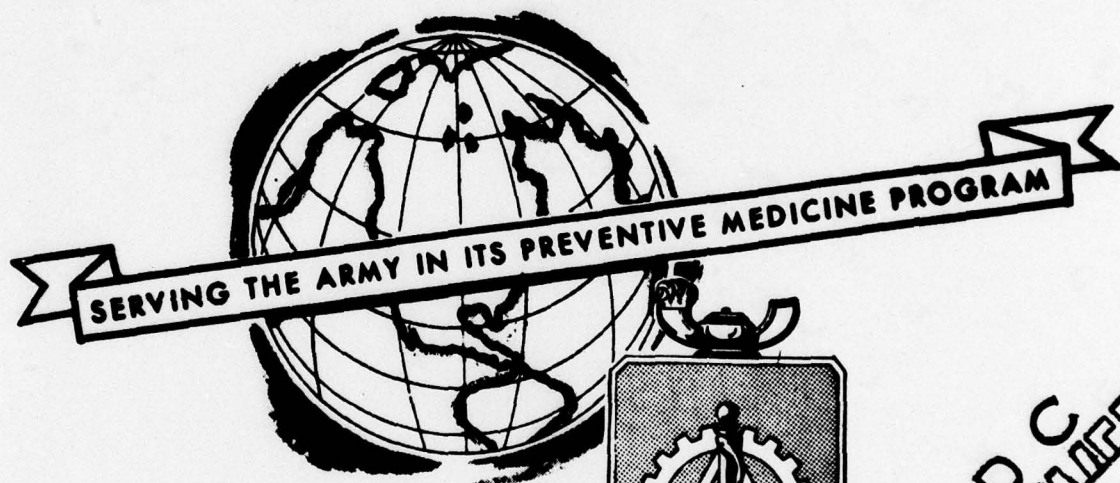
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TOPICAL HAZARD EVALUATION  
OF CANDIDATE INSECT REPELLENT AI3-36542  
1-(CYCLOHEXYLCARBONYL)-1,2,3,6-TETRAHYDROPYRIDINE  
STUDY NO. 51-0818-77  
OCTOBER 1975 - DECEMBER 1976



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20. ABSTRACT (Continue on reverse side if necessary and identify by block number) A hazard evaluation of AI3-36542 was conducted using New Zealand White rabbits for skin and eye studies; Hartley guinea pigs for a skin sensitization study; and Sprague-Dawley, Wistar-derived rats for determination of acute oral toxicity. Technical grade AI3-36542 caused moderate corneal opacity and severe conjunctivitis, while ethanol solutions of this compound caused primary skin irritation. Based on these findings, it is recommended that AI3-36542 not be approved for further testing as a candidate topical insect repellent.		

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DEPARTMENT OF THE ARMY  
U. S. ARMY ENVIRONMENTAL HYGIENE AGENCY  
ABERDEEN PROVING GROUND, MARYLAND 21010

9 MAR 1977

TOPICAL HAZARD EVALUATION  
OF CANDIDATE INSECT REPELLENT AI3-36542  
1-(CYCLOHEXYLCARBONYL)-1,2,3,6-TETRAHYDROPYRIDINE  
STUDY NO. 51-0818-77  
OCTOBER 1975 - DECEMBER 1976

ABSTRACT

A hazard evaluation of AI3-36542 was conducted using New Zealand White rabbits for skin and eye studies; Hartley guinea pigs for a skin sensitization study; and Sprague-Dawley, Wistar-derived rats for determination of acute oral toxicity. Technical grade AI3-36542 caused moderate corneal opacity and severe conjunctivitis, while ethanol solutions of this compound caused primary skin irritation. Based on these findings, it is recommended that AI3-36542 not be approved for further testing as a candidate topical insect repellent.

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TOPICAL HAZARD EVALUATION  
OF CANDIDATE INSECT REPELLENT AI3-36542  
1-(CYCLOHEXYLCARBONYL)-1,2,3,6-TETRAHYDROPYRIDINE  
STUDY NO. 51-0818-77  
OCTOBER 1975 - DECEMBER 1976

1. AUTHORITY.

a. Letter, US Department of Agriculture, Agricultural Research Service, Southern Region, Insects Affecting Man Research Laboratory, Gainesville, FL, 17 October 1975.

b. Memorandum of Understanding Between the US Department of the Army, Office of The Surgeon General, the US Army Health Services Command, The US Army Environmental Hygiene Agency, the Armed Forces Pest Control Board and the US Department of Agriculture, effective December 1970 with Amendment No. 1, effective August 1974.

2. REFERENCE. Toxicology Division Procedural Guide, US Army Environmental Hygiene Agency (USAEHA), 1972.

3. PURPOSE. The purpose of this study was to provide guidance for further entomological testing of the candidate insect repellent AI3-36542.

4. SUMMARY OF FINDINGS. A hazard evaluation of the candidate repellent AI3-36542 [1-(cyclohexylcarbonyl)-1,2,3,6-tetrahydropyridine] was conducted by this Agency using New Zealand White rabbits for skin and eye studies, Hartley guinea pigs for a skin sensitization study, and Sprague-Dawley Wistar-derived rats for determination of oral toxicity. A tabular presentation of animal toxicity data developed in this Agency follows:\*

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\* The experiments reported herein were conducted according to the "Guide for the Care and Use of Laboratory Animals," as prepared by the Committee on Revision of the "Guide for Laboratory Animal Facilities and Care," of the Institute of Laboratory Animal Resources, National Research Council (1972), and were performed in animal facilities fully accredited by the American Association for the Accreditation of Laboratory Animal Care.

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TABULAR PRESENTATION OF DATA

<u>Test</u>	<u>Results</u>	<u>Interpretation</u>
<u>SKIN IRRITATION STUDIES</u>		
<u>Rabbits</u> Single 24-hour application to intact and abraded skin of New Zealand White rabbits.	Compound AI3-36542 produced no primary irritation of the intact skin or of the skin surrounding an abrasion.	USAEHA Category I (ref Appendix).
0.5 ml technical grade compound applied to each of six rabbits.		
<u>EYE IRRITATION STUDIES</u>		
<u>Rabbits</u> Single 24-hour application of 0.1 ml technical grade compound to one eye of each of six New Zealand White rabbits.	Compound AI3-36542 produced moderate injury to the cornea and, in addition, some injury to the conjunctiva.	USAEHA Category E (ref Appendix).
	No signs at 7 days.	
<u>APPROXIMATE LETHAL DOSE (ALD)</u>		
<u>Oral</u>		
Rats (male) - no diluent	ALD = 2200 mg/kg	Presents little lethal hazard from acute accidental ingestion.

Test	Results	Interpretation
<u>SENSITIZATION STUDIES</u>		
<u>Guinea Pigs (male)</u>		
Intradermal injections of 0.1 ml of a 0.1 percent suspension (W/V) of AI3-36542 or dinitrochlorobenzene (DNCB)* in a mixture containing 1 volume of propylene glycol and 29 volumes of saline.		
Ten test guinea pigs received and challenged with a 0.1 percent solution of AI3-36542.	Challenge dose of test compound (last intradermal injection) did not produce a sensitization reaction.	Compound AI3-36542 did not produce a sensitization reaction under these conditions and is not expected to produce a sensitization reaction in man.
Ten positive control guinea pigs received and challenged with 0.1 percent suspension of DNCB.	Positive control (DNCB) produced a marked sensitization reaction in ten out of ten guinea pigs.	
Ten cage control guinea pigs; five receiving challenge dose of test compound without prior sensitizing dose, and five receiving challenge dose of DNCB without prior sensitizing dose.		

\* A known skin sensitizer.

Test	Results	Interpretation
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PHOTOCHEMICAL SKIN IRRITATION STUDIES

Rabbits

A single application (0.05 ml) of a 25 percent (W/V) solution of AI3-36542 and of a 10 percent (W/V) oil of Bergamot solution (positive control) in 95 percent ethyl alcohol, were applied to the intact skin of six rabbits. Five minutes after application, the rabbits were exposed to ultraviolet (UV) light (365 nm) for 30 minutes at a distance of 10-15 cm.

Following UV exposures of the rabbits, 0.05 ml of test compound and diluent were applied to additional skin areas to serve as unirradiated control sites. Each area was graded for skin irritation reactions at 24, 48 and 72 hours after application.

AI3-36542 did not cause a photochemical irritation reaction under test conditions. However, ethanol solution of AI3-36542 caused the same degree of erythema and edema at both irradiated and non-irradiated skin sites. Positive control application and irradiation caused greater irritant effects than in unirradiated areas.

Compound AI3-36542 did not cause a photochemical irritation reaction under test conditions but ethanol solutions of the compound may cause a skin irritation reaction in humans.

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5. CONCLUSIONS. Technical grade AI3-36542 caused moderate injury to the cornea, severe injury to the conjunctiva of the rabbit and may cause similar damage if it should accidentally enter the eye of man.

6. RECOMMENDATIONS. Under the provisions of the Memorandum of Understanding (reference paragraph 1b), it is recommended that AI3-36542 not be approved for further testing as a candidate insect repellent.

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APPENDIX

TOPICAL HAZARD EVALUATION PROGRAM  
DEFINITIONS OF CATEGORIES OF COMPOUNDS BEING  
CONSIDERED FOR ACUTE SKIN APPLICATIONS

CATEGORY I - Compounds producing no primary irritation of the intact skin or no greater than mild primary irritation of the skin surrounding an abrasion. (INTERPRETATION: No restriction for acute application to the human skin.)

CATEGORY II - Compounds producing mild primary irritation of the intact skin and the skin surrounding an abrasion. (INTERPRETATION: Should be used only on human skin found by examination to have no abrasions or may be used as a clothing impregnant.)

CATEGORY III - Compounds producing moderate primary irritation of the intact skin and the skin surrounding an abrasion. (INTERPRETATION: Should not be used directly on the skin without a prophetic patch test having been conducted on humans to determine irritation potential to human skin. May be used without patch testing, with extreme caution, as clothing impregnants. Compound should be resubmitted in the form and at the intended use concentration so that its irritation potential can be reexamined using other test techniques on animals, prior to human testing.)

CATEGORY IV - Compounds producing moderate to severe primary irritation of the intact skin and of the skin surrounding an abrasion and, in addition, producing necrosis, vesiculation and/or eschars. (INTERPRETATION: Should be resubmitted for testing in the form and at the intended use concentration. Upon resubmission, its irritation potential will be reexamined using other test techniques on animals, prior to possible prophetic patch testing in humans, at concentrations which have been shown not to produce primary irritation in animals.)

CATEGORY V - Compounds impossible to classify because of staining of the skin or other masking effects owing to physical properties of the compound. (INTERPRETATION: Not suitable for use on humans.)

EYE CATEGORIES:

A. Compounds noninjurious to the eye. INTERPRETATION: Irritation of human eyes is not expected if the compound should accidentally get into the eyes, provided it is washed out as soon as possible.

B. Compounds producing mild injury to the cornea. INTERPRETATION: Should be used with caution around the eyes.

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C. Compounds producing mild injury to the cornea, and in addition some injury to the conjunctiva. INTERPRETATION: Should be used with caution around the eyes and mucosa.

D. Compounds producing moderate injury to the cornea. INTERPRETATION: Should be used with extreme caution around the eyes.

E. Compounds producing moderate injury to the cornea, and in addition producing some injury to the conjunctiva. INTERPRETATION: Should be used with extreme caution around the eyes and mucosa.

F. Compounds producing severe injury to the cornea and to the conjunctiva. INTERPRETATION: Should be used with extreme caution. It is recommended that use be restricted to areas other than the face.